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Practitioner's Docket No. U 014338-7 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: DILIP G. **SAOJI**, et al.
Serial No.: 10/749,933 Group No.: 1615
Filed: December 31, 2003 Examiner.: --
For: BENZOQUINOLIZINE-2-CARBOXYLIC ACID-CONTAINING COMPOSITIONS

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: India

Application Number: 1170/MUM/2002

Filing Date: December 31, 2002

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)

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Date: May 20, 2004

JANET I. CORD
(type or print name of person certifying)

SIGNATURE OF PRACTITIONER

Reg. No. 33,778

JANET I. CORD
(type or print name of practitioner)

Tel. No.: (212) 708-1935

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c/o Ladas & Parry LLP
26 West 61st Street
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NOTE: *"The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63."* 37 C.F.R. 1.55(a).

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Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 31/12/2002 in respect of Patent Application No. 1170/MUM/2002 of Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai – 400 051, Maharashtra State, India, an Indian Company registered under the Companies Act, 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 19th day of March 2004.

(N.K.GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5(2), 7, 54 and 135 and rule 33A]

1. We, Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India an Indian Company registered under the Companies Act 1956

2. hereby declare:-

a) that we are in possession of an invention titled 'A Process for Benzoquinolizine-2-carboxylic acid - containing compositions'

ORIGINAL

b) that the Provisional Specification relating to this invention is filed with this application.

c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventor (s) for the said invention are:

a) Dr. Noel John de Souza, Dr. Milind Chintaman Shukla, Dr. Dilip Gopalkrishna Saoji, Dr. Mahesh Vithalbhai Patel

b) Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India.

c) All Indian National

4. We, claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

Not applicable

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/we are the applicant/patentee:

1170 | मुंबई MUM | 2002 Not applicable.

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on ____ under section 16 of the Act.

31 दिसम्बर DEC 2002 Not applicable.

7. That we are the assignee or legal representative of the true and first inventors.

1170/mum/2002
31/12/2002

8. That our address for service in India is as follows:

Wockhardt Limited
Wockhardt Towers
Bandra-Kurla Complex
Bandra (E)
MUMBAI 400 051
Tel. No. 022-6534444
Fax 022-6534242

9. Following declaration was given by the inventor(s):

We the true and first inventors for this invention declare that the applicant Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051 herein is our assignee.

Dr. Noel John de Souza _____

Dr. Milind Chintaman Shukla _____

Dr. Dilip Gopalkrishna Saoji _____

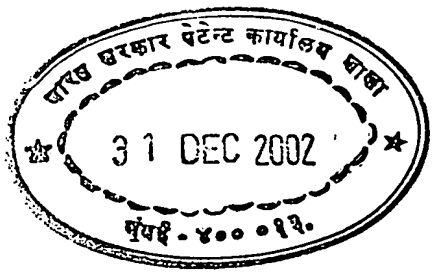
Dr. Mahesh Vithalbhai Patel _____

Dated this 30th day of December 2002

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application:

a) Provisional specification – 3 copies
b) Form 2
c) Form 3



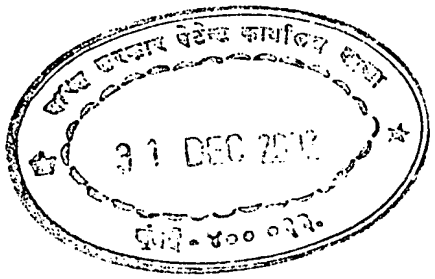
We request that a patent may be granted to us for the said invention.

Dated this 30th day of December 2002

DR N J de SOUZA
DIRECTOR-R&D

To

The Controller of Patents,
The Patents Office Branch, Mumbai.



A PROCESS FOR BENZOQUINOLIZINE-2-CARBOXYLIC ACID - CONTAINING COMPOSITIONS

FIELD OF THE INVENTION

This invention relates to topical compositions of an antibacterial benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in hitherto undescribed pharmaceutical compositions, or as an ingredient in novel combination with at least one agent selected from a retinoid, an antifungal agent, another antibacterial compound and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

BACKGROUND OF THE INVENTION

Topical compositions are useful for a wide range of dermal infection-originating disorders, ranging from those that are skin-related to those that are related to specific body parts, such as ophthalmic, otic and nasal disorders. The incidence and epidemiology of these different disorders is well documented in the scientific and patent literature.

The use of a benzoquinolizine-2-carboxylic acid antibacterial to treat infections represents the current state of the art in the field of dermal pharmaceutical compositions and methods of treatment. For example, a topical dermal composition containing the benzoquinolizine-2-carboxylic acid, RS-(+/-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H benzo [i,j] quinolizine-2-carboxylic acid, is marketed by Wockhardt Limited, India under the name NADOXIN.TM.(Nadifloxacin 1 %) Cream.

Although nadifloxacin, from chemical considerations, belongs to the class of benzoquinolizine-2-carboxylic acids, it is classified from considerations of its antibacterial mode of DNA gyrase inhibition and its common quinolone core moiety, as a quinolone antibacterial, with its given name analogous in terminology to drugs like ciprofloxacin and levofloxacin.

Nadifloxacin has also been utilized in other dermal antibiotic compositions:

ACUATIM.TM Cream, Otsuka Pharmaceuticals, Japan
ACUATIM.TM.Lotion, Otsuka Pharmaceuticals, Japan
and by Galderma, France.

In the field of ophthalmic pharmaceutical formulations and methods of treatment, the current state of the art embraces the use of quinolone antibiotics such as ciprofloxacin, ofloxacin, norfloxacin, and lomefloxacin as outlined in US Patent 6,395,476 and PCT /US 99/22625, the contents of which are incorporated herein by reference.

Among benzoquinolizine-2-carboxylic acids reported to have therapeutically and/or prophylactically useful antibiotic, in particular antibacterial, effect are those illustratively disclosed in the following patents and patent applications, each of which is individually incorporated herein by reference:

US Patent No. 4,399,134;
US Patent No. 4,552,879;
Chem. Pharm. Bull. 44 (1996), 642-5;
Indian Application 417/MUM/2000 filed on May 8,2000;
US Application No. 09/566,875 filed on May 8, 2000;
PCT Application No. PCT/IN00/00054 filed on May 8, 2000;
US Application No. 09/640,947 filed on August 17, 2001;
PCT Application No. PCT/IN00/00111 filed on Nov. 2000;
US Application No. 09/802,793 filed on March 9, 2001;
PCT Application No. PCT/IN01/00097 filed on May 3, 2001;
US Application No. 09/850,669 filed on May 8, 2001;
PCT Application No. PCT/IN01/00100 filed on May 8, 2001;
US Application No. 10/156,685 filed on May 28, 2002; and
PCT Application No. PCT/IN02/00123 filed on May 28, 2002

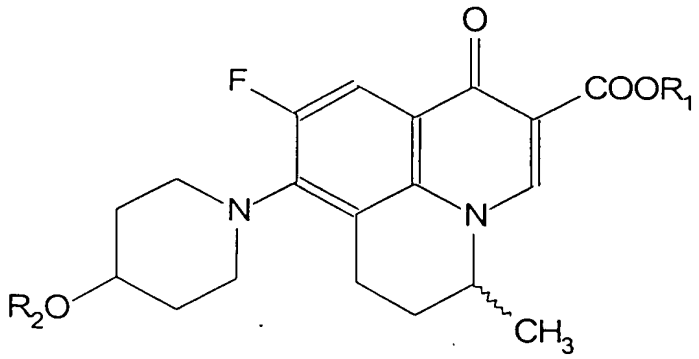
Compounds disclosed in the above-cited Indian and US patents and patent applcations include for instance,

RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid, also referred herein as RS-(±)-nadifloxacin or nadifloxacin.

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid also referred to herein as S-(-)-nadifloxacin,

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt, also referred to herein as S-(-)-nadifloxacin arginine salt.

RS-(±)-nadifloxacin has the structure shown in Formula I



I

where R1 = R2 = H.

RS-nadifloxacin and S-nadifloxacin, in particular, exhibit strong antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria, resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), quinolone-resistant *Staphylococcus aureus,* coagulase negative staphylococci, such as methicillin-resistant *Staphylococcus epidermidis* (MRSE), enterococci, betahemolytic streptococci and viridans group of streptococci, mycobacteria and newly emerging nosocomial pathogens such as *Chryseobacterium meningosepticum,* and Gram-negative pathogens such as *E.coli, Klebsiella, Proteus, Serratia, Citrobacter* and *Pseudomonas.*

Many Gram-positive organisms have developed significant levels of resistance to other antibiotics. About 65% of all cases of bacterial keratitis and about 85% of all cases of bacterial conjunctivitis are attributable to infection by gram-positive organisms such as those listed above. The causative organism of acne vulgaris is *Propionibacterium acnes.* The incidence of acne vulgaris is very high, specially among adolescents. Among new emerging diseases are pyoderma gangrenosum and necrotising fascitis. Pyoderma gangrenosum is a

chronic destructive ulcerating wound disorder of unknown etiology, and pathophysiology. *S. aureus* is most often the infecting microorganism. Necrotising fascitis is a life threatening bacterial infection causing necrosis of the fascia, underlying skin and vasculature. It progresses rapidly, has a frightening 74% mortality and a high risk of systemic activity. The Group A beta-hemolytic streptococci (GABHS) are frequently identified in necrotising fascitis. However, the infection is commonly polymicrobial in etiology (Geeham & Pembeton 1997), other causative enzymes including *Peptococcus E.coli Pseudomonas, S. pyogenes, S. marcescens* (Douglas 1996, Gillen 1995). Bacterial resistance to antibiotics is an increasingly recurrent phenomenon. The need for pharmaceutical compositions specifically to treat infections arising from such emerging and resistant microorganisms thus assumes urgent significance.

The etiology of acne, its epidemiology, its psychosocial effects leading to impaired academic and social functioning, its effects on employment status, its consequences on the overall well-being and quality of life of the patient with acne, and the aims of treating it are well described in US 5,543,417 and 6,365,623 B1 and references contained therein, all of which are included herein by reference. Acne is a disease with multifactorial pathogenesis including among other factors that of proliferation of *Propionibacterium acnes*. Among conventional topical treatments such as the antibiotics erythromycin and esters thereof, neomycin, clindamycin and esters thereof, tetracycline or the more recent nadifloxacin, and anti-seborrhoeic or keratolytic agents such as benzoyl peroxide, salicylic acid, azelaic acid used for the removal of comedones in acne, are the topical retinoids such as tretinoin, isotretinoin and those listed in US Patent 4,717,720, US Patent 5,587,367 and US Patent 6,462,064 and references contained therein, all of which are included herein by reference. US patent 5,587,367 discloses a pharmaceutical or cosmetic dermal composition containing a combination of a retinoid with a second agent, such a second agent being a sterol.

The compositions of this invention comprise a combination of an antibacterial benzoquinolizine-2-cartboxylic acid such as herein described and a retinoid such as herein described resulting in a synergistic effect for the treatment of epidermic keratinization disorders, epithelial or epidermic proliferation disorders and/or disorders of the sebaceous function, for instance disorders selected from the group consisting of acne vulgaris,

comedonic or polymorphic acne, acne rosaria, nodulocystic acne, acne conglobata, senile acne and secondary acnes.

Allergic inflammatory conditions of the skin are manifested by macules, papules or raised wheals involving part/s of the body. At cellular level there is a breakdown of phospholipids in the cell membrane and this gives rise to mediators like leukotrienes, platelet activating factor, prostaglandins and histamine. A steroid is generally administered to alleviate the symptoms of erythema, the immune response and the related itching which are normally associated with the above-mentioned group of bacterially-infected or invaded immunologic and/or allergic inflammatory dermal disorders. It is undesirable to use steroids alone for topical treatment for extended periods of time. Steroids can penetrate the skin and cause undesirable effects, including skin atrophy, suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, glycosuria, hyperglycemia, etc. Combinations of antibacterials and steroids are disclosed in US Pat. Nos. 4,604,384, WO 2002/039993, WO 02/30395 A1, WO 00/18404, US 6,395,746, and WO 00/18404.

Fungal diseases refer to fungal infections, including yeast infections, of keratinized and non-keratinized epithelial tissues, for example skin, nails, mucosa and the like and includes tinea pedis, tinea capitis, tinea corporis, tinea versicolor, nail fungal diseases (distal subungual onychomycosis caused by dermatophyte infection), scalp disorders, tinea cruris, and candidiasis (cf. US 6,075,056, incorporated herein by reference). Antifungal agents are useful in treating dermatophytoses such as trichophytid, endodermophytosis, favid and deepseated trichophytid and fungal infections such as mucocutaneous mycosis and deep-seated candidiasis (cf. WO 2000062776, incorporated herein by reference).

None of the references cited above specifically contemplates formulating a benzoquinolizine-2-carboxylic acid antibiotic in topical combination compositions using one or more ingredients selected from the group of a retinoid, an antibacterial, a steroid / non-steroid antiinflammatory agent and/or an antifungal agent.

None of the references cited above specifically contemplates formulating a benzoquinolizine-2-carboxylic acid antibiotic in a combination therapy or coformulation of a benzoquinolizine-2-carboxylic acid antibacterial agent having a high degree of activity against gram-positive

bacterial with one or more antibacterial agents effective against gram-negative bacteria and/or with a retinoid, steroid/non-steroid antiinflammatory agent and/or antifungal agent.

SUMMARY OF THE INVENTION

It is an aspect of this invention to provide topical compositions of an antibacterial benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in pharmaceutical compositions, or as an ingredient in combination with at least one agent selected from the group of a retinoid, an antifungal agent, an antibacterial and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

DETAILED DESCRIPTION OF THE INVENTION

Any benzoquinolizine-2-carboxylic acid, antimicrobial drug or one of its chiral isomers i.e. one having a benzoquinolizine-2-carboxylic acid moiety as part of its chemical structure, can be formulated in a composition either as a single ingredient or in combination with one or more ingredients selected from the group of retinoid, an antifungal agent, an antibacterial and/or a steroid/non-steroid anti-inflammatory agent in accordance with the invention and acceptable carriers.

One embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal compositions with at least one adjunct retinoid ingredient resulting in a synergistic effect for the treatment of epidermic keratinization disorders, epithelial or epidermic proliferation disorders and/or disorders of the sebaceous function, for instance disorders selected from the group consisting of acne vulgaris, comedonic or polymorphic acne, acne rosaria, nodulocystic acne, acne conglobata, senile acne and secondary acnes.

Another embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal compositions with at least one steroid ingredient resulting in a

synergistic effect for the treatment of bacterially infected or invaded immunologic and/or allergic inflammatory disorders, for instance selected from the group consisting of contact dermatitis, seborrhoeic dermatitis, erythema multiformae, pyodermic-related wounds and infective eczema and ophthalmic, otic or nasal disorders. The formulation of this invention has the advantages of combining an agent useful for treating the dermal and other body part/s bacterial diseases and disorders with a steroid capable of reducing the associated inflammation, with the ability to rapidly eradicate bacterial infections and eliminate the symptoms thereof, and as a consequence minimize the risk of undesirable side effects. Such a formulation would ideally deliver the antibacterial agent and the steroid to the skin and other body part/s, and maintain the combination on the skin and other body part/s for the period of time necessary to effect treatment, but minimize the penetration of the skin or other body part/s with respect to the active ingredients, thus avoiding the potential steroid effects noted above.

Still another embodiment of this invention relates to antibacterial benzoquinolizine-2-carboxylic acid-containing dermal and other body part/s compositions with at least one antifungal agent ingredient resulting in a synergistic effect for the treatment of bacterially infected fungal diseases.

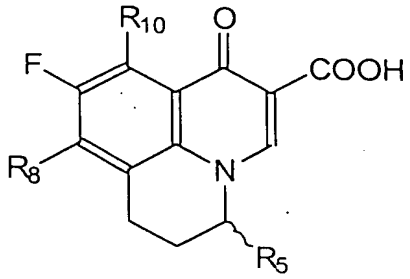
An antifungal agent is any agent that prevents the growth of or kills a fungal organism such as antifungal polyene macrolides such as amphotericin B, and nystatin, azole antifungal agents such as clotrimazole, miconazole, and ketoconazole, arylmethylamine antifungal agents such as butenafine and terbinafine (cf. EP 0310122B1, incorporated herein by reference), fluorinated pyrimidines, halogenated phenolic ethers, thiocarbamates, allylamines, benzylamines. In addition, antifungal agents can be agents that interpolate fungal cell wall components or act as cell wall inhibitors. Specific antifungal agents within the scope of the invention include, without limitation, the squalene epoxidase inhibitor, butenafine, and the ergosterol biosynthesis inhibitor, miconazole.

Still another embodiment of this invention relates to an antibacterial benzoquinolizine-2-carboxylic acid-containing dermal and other body part/s compositions with at least one antifungal agent ingredient and at least one steroid resulting in a synergistic effect for the treatment of bacterially infected, inflammatory fungal diseases. WO 99/20261 (incorporated

herein by reference) describes inflammation of mucosal tissue, fungus-induced mucositis and rhinositis, other fungus-induced mucositis conditions such as chronic otitis media, and methods and materials for treating them. Topical compositions are described for psoriatic infections (WO 9949835, incorporated herein by reference), and for cutaneous mycosis including candidiasis, vulvitis, etc., (JP 07233088 (incorporated herein by reference).

The subject antibiotic benzoquinolizine-2-carboxylic acid compounds, including but not limited to nadifloxacin, S-nadifloxacin, S-nadifloxacin arginine salt, can be formulated as a gel or cream for topical application to skin.

Preferred benzoquinolizine-2-carboxylic acid are compounds having Formula-II

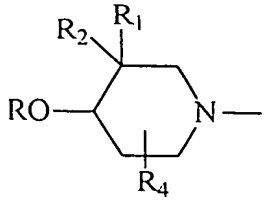


Formula-II

Preferably R_5 is C_{1-6} alkyl, and more preferably R_5=CH_3, as a mixture of enantiomers or in a stereochemical orientation .

Preferably R_8 is 4-hydroxypiperidinyl optionally further substituted with one or more C_{1-6} alkyl, hydroxypiperidinyl optionally further mono/poly substituted with C_{1-6} alkyl.

More preferably R_8 is



wherein

R is hydrogen, or C_1-C_6 alkyl as hereinbefore defined, or glycosyl, or aralkyl such as benzyl, or C_1-C_6 alkanoyl such as acetyl, propionyl, pivaloyl, or aminoalkanoyl such as amino acid residues derived from one of the 20 naturally occurring amino acids viz. alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, or the optically active isomers thereof, or the racemic mixtures thereof, or $C_6H_{11}O_6$, PO_3H_2 or SO_3H thus giving respectively the gluconic acid, phosphoric acid and sulfonic acid ester derivatives of the compounds.

R_1 and R_2 are the same or different and represent H, C_{1-4} alkyl, aralkyl, aminoalkyl, trifluoroalkyl, or halogen,

R_4 = H, C_{1-4} alkyl, CF_3, phenyl, or F, R4 is present at one or more of the positions of 2-, 4-, 5-, or 6- of the piperidine ring;

R_{10} is H, C_{1-5} alkyl, amino, alkylamino, acylamino

or an optical isomer, diastereomer or enantiomer thereof, or polymorphs and pseudopolymorphs or prodrugs thereof or pharmaceutically acceptable salts and hydrates thereof.

"Optical isomer", "stereoisomer", and "diastereomer" as referred to herein have the standard art recognized meanings.

Examples of preferred benzoquinolizine-2-carboxylic acid are compounds selected from RS-(±)-, R-(+)- or S-(-)- 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid arginine salt and polymorphic forms thereof, RS-(±)-, R-(+)- or S-(-)- 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid 0.2 hydrate, RS-(±)-, R-(+)- or S-(-)- 9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-{trans-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-{cis-4-(RS)-hydroxy-3-(RS)-methylpiperidin-1-yl-5-methyl- -oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-

{cis-(-)-4-R-hydroxy-3-S-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-{cis-(+)-4-S-hydroxy-3-R-methylpiperidin-1-yl}-5-methyl-1-oxo-1H,5H-benzo[i, j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(3-ethyl-4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid (mixture of cis racemate and trans racemate) and pure stereoisomers thereof,
RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid, also referred herein as RS-(±)-nadifloxacin,

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid also referred to herein as S-(-)-nadifloxacin,

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid arginine salt, also referred to herein as S-(-)-nadifloxacin arginine salt.

Benzoquinolizine compounds used in compositions of the invention can be prepared by a process known per se, by processes described in the patents included herein by reference disclosing such drugs.

US Application No. 09/566,875
US Application No. 09/640,947
US Application No. 09/802,793,
US Application No. 09/850,669
US Application No. 10/156,685
US Patent No. 4,399,134
US Patent No. 4,552,879

Antibiotics that can be used in combination with an antibacterial benzoquinolizine-2-carboxylic acid compound include but are not limited to:
Polymyxin Sulphate(Gram -ve)
Bacitracin

Gramicidin and
Colistin Sulphate(Gram -ve).

Retinoids, antiacne agents, steroids (glucocorticoids) and antifungal agents that can be used in the compositions of this invention include but are not limited to:
Retinoids: Benzoyl peroxide, Dichloroacetic acid, Glutaraldehyde, Resorcinol, Retinoic acid and Salicylic acid.

Antiacne: Adapalene, Algestone acetophenide, Azelaic acid, Benzoyl peroxide, Cioteronel, Cyproterone, Isotretinoin, Motretinide, Resorcinol, Retinoic acid, Tretinoin, Tazarotene and Tioxolone.

Glucocorticoid: 21-acetoxypregnnolone, Alclometasone, Algestone, Amcinonide, Beclomethasone, Betamethasone, Budesonide, Chloroprednisone, Ciclesonide, Clobetasol, Clobetasone, Clocortolone, Cloprednol, Corticosterone, Cortisone, Cortivazol, Deflazacort, Desonide, Desoximetasone, Dexamethasone, Diflorasone, Diflucortolone, Difluprednate, Enoxolone, Fluazacort, Flucloronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Fluocinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednidene acetate, Fluprednidene acetate, Fluprednisolone, Flurandrenolide, Fluticasone propionate, Formocortal, Halcinonide, Halobetasol propionate, Halometasone, Halopredone acetate, Hydrocortamate, Hydrocortisone, Loteprednol etabonate,Mazipredone, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisolone, Prednisolone 21-diethylaminoacetate, Prednisolone sodium phosphate, Predisone, prednival, Prednylidene, Rimexolone, Tixocortol, Triamcinolone, Triamcinoloneacetonide, Triamcinolone benetonide, Triamcinolone hexacetonide.

Antifungal (Antibiotics): Polyenes: Amphotericin, Candicidin, Dermostatin, Filipin, Fungichromin, Hachimycin, Hamycin, Lucensomycin, Mepartricin, Natamycin, Nystatin, Pecilocin, Perimycin, Azaserine, Caspofungin, Griseofulvin, Oligomycins, Pyrrolnitrin, Siccanin, Tubercidin, Viridin.

Antifungal (Synthetic): Allylamines: Butenafine, Naftifine, Terbinafine
Imidazoles: Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole,

Clotrimazole, Econazole, Enilconazole, Fenticonazole, Flutrimazole, Isoconazole, Ketoconazole, Lanoconazole, Miconazole, Neticonazole, Omoconazole, Oxiconazole nitrate, Sertaconazole, Sulconazole, Tioconazole.
Thiocarbamates: Liranaftate, Tolciclate, Tolindate, Tolnaftate
Triazoles: Fluconazole, Itraconazole, Posaconazole, Saperconazole, Terconazole, Voriconazole.

Others: Acrisorcin, Amorolfine, Biphenamine, Bromosalicylchloranilide, Buclosamide, Calcium propionate, Chlorphenesin, Ciclopirox, Cloxyquin, Coparaffinate, Diamthazole dihydrochloride, Exalamide, Flucytosine, Hexetidine, Loflucarban, Nifuratel, Potassium iodide, Propionic acid, Pyrithione, Salicylanilide, Sodium propionate, Sulbentine, Tenonitrozole, Triacetin, Undecylenic acid, Zinc propionate

The preferred retinoid is adapalene.
The preferred steroid is clobetasol or mometasone, in particular, clobetasol propionate.
The preferred antifungal agent is butenafine.

The compositions of the invention contain other than the benzoquinolizine-2-carboxylic acid and/or one of its combination partners mentioned above, a pharmaceutical vehicle compatible with an administration by a topical method (skin and mucous), ocular or otic or nasal.

For topical application, the pharmaceutical or cosmetic compositions of the invention comprise the vehicles and ingredients required to provide the composition, for example, in the form of ointments, creams, milks, pomades, powders, impregnated pads, solutions, gels, sprays, shampoos, washing lotions or even suspensions, microspheres or nanospheres, lipidic or polymeric vesicles or polymeric patches.

For ocular administration, the composition of the invention is provided in the form of eyedrops or eyewashes.

Generally the composition is applied one or more times per day on the area to be treated. The number of times a time per day that the composition is applied depends on the severity of the condition and the advice of the physician.

The invention also has for an object the use of the ingredients of the invention in the preparation of a pharmaceutical or cosmetic composition intended principally for the treatment or correction of epidermic keratinization disorders, any other disorder or any other functional defect or excess of epidermic or epithelial proliferation. The composition thus prepared can serve to treat the disorders mentioned above, having or not an inflammatory and/or immunoallergic component, comprising conjunctive tissue degeneration disorders and benign or malignant tumors, to combat against skin aging, to favor cicatrization or to improve the appearance of the skin of persons exhibiting keratinization disorders or suffering from seborrhea.

In particular, the combination described in the present invention is intended:

for the treatment of dermatologic ailments linked to a keratinization disorder causing differentiation and proliferation and principally for treating common acne, comedons, polymorphs, nodulokystic acne, conglobuta, senile acne, secondary acne such as solar, medicinal and professional acne;

for the treatment of other types of keratinization disorders, principally ichthyoses, ichthyosiform conditions, Darier malady, palmoplantary keratodermies, leucophasies and leucoplasiform conditions as well as lichen;

for the treatment of dermatologic ailments linked to a keratinization disorder having an inflammatory and/or immunoallergic component and principally, all forms of psoriasis, be they cutaneous, mucous or ungual, and even psoriasic rheumatism, or again cutaneous atopies, such as eczema;

for the treatment of other dermatologic disorders such as blistery dermatoses and collagen maladies;

to prevent or heal scars of epidermic and/or dermic atrophy, induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;

for the treatment of certain ophthalmologic disorders, principally corneopathies;

to combat against disorders of the sebaccous function such as hyperseborrhea of acne or simple seborrhea;

to combat impetigo folliculitis, infected dermatitis, wounds and burns, pyoderma gangrenosum and necrotising fascitis.

The compositions of the invention are also useful in the cosmetic field, in particular in body hygiene, and also capillary hygiene (action against seborrhea).

Ophthalmic Compositions

In accordance with another aspect of the invention, the compositions comprise a benzoquinolizine-2-carboxylic acid component. The compositions may also contain a second ingredient in accordance with the invention. The benzoquinolizine-2-carboxylic acid component is present in an amount effective as a antibiotic when the composition is placed in a mammalian eye. The carrier component is present in an amount effective to act as a carrier for the benzoquinolizine-2-carboxylic acid component, and other active component or components, if present, in the composition, and preferably is ophthalmically acceptable.

In one very useful embodiment, the present compositions comprise a benzoquinolizine-2-carboxylic acid component, a combination partner component, and a carrier component effective to act as a carrier for the benzoquinolizine-2-carboxylic acid and a combination partner components. The benzoquinolizine-2-carboxylic acid component is effective as an antibiotic, as described elsewhere herein. The combination partner component is present in an amount effective to reduce at least one of inflammation and pain when the composition is placed in a mammalian eye.

Very useful compositions and results are obtained when the benzoquinolizine-2-carboxylic acid component is one of the aforementioned preferred compounds of the invention.

The combination partner components included in the present compositions preferably are the aforementioned preferred combination partners.

The present carrier components may contain one or more pharmaceutically or ophthalmically acceptable ingredients, for example, tonicity adjuster components, buffer components, viscosity components, lubricity components, surfactant components and the like, conventionally used, for example, in ophthalmic formulations. Preferably, the compositions have pH's in the physiological range of human beings, for example, in the range of about 4 to about 8.5.

The present compositions may be in any form suitable for effective administration to the human or animal to be treated. Preferably, the compositions are present in a form selected from solutions, suspensions, gels, ointments solids and the like which are very effective for ocular administration. The carrier component may conveniently be selected and/or compounded to provide the composition in the form desired. The compositions are formulated to include an amount of the active ingredient(s) sufficient to treat or prevent the intended condition.

Methods of using these compositions are included in the scope of the present invention. Such methods comprise administering to a human or animal, preferably to a mammalian eye, a therapeutically effective amounts of the compositions as described herein. Such methods provide one or more benefits to the human or animal treated in accordance with the present methods. For example, such benefits include prevention, control or management of microbial infections, and reduction in inflammation and/or pain. Some compositions of this invention do not include preservatives. This reduces the risk of irritation and/or other detrimental or unpleasant side effects in the human or animal being treated.

Any and all features described herein and combinations of such features are included within the scope of the present invention provided that the features of any such combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are in the following detailed description and Examples and claim.

The present compositions include an antibiotically effective amount of the benzoquinolizine-2-carboxylic acid component. Such amounts may vary over a relatively broad range

depending, for example, on the specific form of the composition being used, the specific benzoquinolizine-2-carboxylic acid component being used, the specific application for the composition, the frequency of use of the composition and the like factors.
The benzoquinolizine-2-carboxylic acid component may be any benzoquinolizine-2-carboxylic acid derivative which is acceptable or suitable for administration to the eye and has at least a portion, preferably a major portion or at least about 50% of the antibiotic effectiveness of the basic benzoquinolizine-2-carboxylic acid in the present composition in the mammalian eye. The present benzoquinolizine-2-carboxylic acid component may be selected from the benzoquinolizine-2-carboxylic acid itself or benzoquinolizine-2-carboxylic acid hydrates or ophthalmically acceptable salts of such benzoquinolizine-2-carboxylic acid, for example, including acid addition salts such as hydrochlorides, maleates, pamoates and the like, and alkali metal salts such as sodium and potassium salts, base salts, basic aminoacid salts such as arginine salts and mixtures thereof and the like.

The present carrier components may be selected from pharmaceutically acceptable organic and/or inorganic components which, preferably, in the present compositions are ophthalmically acceptable. As used herein, the term "ophthalmically acceptable" refers to a material which, at the concentration or amount in question, is compatible with ocular tissue, that is the material does not cause significant or undue detrimental effects when brought into contact with ocular tissue. The carrier component preferably is ophthalmically acceptable. Preferably, each component of the present compositions is also compatible with the other components of the compositions.

Examples of suitable materials useful in the present carrier components include water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum-based jelly, ethyl cellulose, ethyl oleate, carboxymethyl cellulose, polyvinylpyrrolidone, isopropyl myristate, other conventionally employed pharmaceutically acceptable materials and the like. To facilitate solubilisation, cyclodextrins may be used, such as for example hyrdoxypropyl cyclodextrin, or aminoacids may be used, such as for example arginine.

The carrier component may also include auxiliary substances such as emulsifiers, wetting agents, bodying agents, buffer components, acids and/or bases, tonicity adjuster components,

surfactant components, viscosity agents, lubricity components, other materials useful in ophthalmic formulations and the like.

Examples of optionally useful bodying agents include, but are not limited to, various polyethylene glycols, carbowaxes, petroleum jelly and the like.

Suitable buffers include, but are not limited to, inorganic buffers such as phosphate buffers, borate buffers and the like, and organic buffers, such as acetate buffers, citrate buffers, tromethamine and the like.

Tonicity adjusters optionally useful in the present compositions include, but are not limited to, dextrose, potassium chloride and/or sodium chloride and the like, is preferably sodium chloride.

Acids optionally useful in the present compositions include boric acid, hydrochloric acid, acetic acid, other acids which are ophthalmically acceptable in the concentrations used, and the like.

Bases which may be included in the present compositions include, but are not limited to, sodium and/or potassium hydroxides, other alkali and/or alkaline earth metal hydroxides, organic bases, basic aminoacids such as arginine, other bases which are ophthalmically acceptable in the concentrations used, and the like.

The acid/bases/buffers preferably are included, if at all, to provide and/or maintain the present compositions at a pH in the physiologically acceptable range, more preferably in a range of about 4 to about 8.5, still more preferably about 6 to about 8, and especially about 6.8 to about 8.

Surfactant components optionally useful in the compositions of the present invention include, but are not limited to, lipoprotein detergents that when present in the compositions reduce the surface tension between the compositions and the eye (lacrimal) fluid. Preferably, nonionic surfactants are used.

Viscosity agents optionally useful in the compositions of the present invention include, but are not limited to, carbopol, cellulose derivatives such as hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, other viscosity inducing materials useful in ophthalmic formulations and the like.

Lubricity components optionally useful in the compositions of the present invention include, but are not limited to, polyvinyl alcohol, polyvinylpyrrolidone, carbopol and the like.
The present compositions may include effective amounts of chelating or sequestering components, such as ethylene diamine tetraacetic acid (EDTA), citric acid, tartaric acid and the like. In one useful embodiment, the present compositions are substantially free of EDTA.

Other optional excipients useful in the present compositions include stabilizing agents such as antioxidants, for example, alkali metal metabisulfates, ascorbic acid and the like.

The carrier component may be in various forms. In one embodiment, the carrier component comprises a liquid, and the composition may be a solution or a suspension. In either situation, the carrier may simply contain water and one or more auxiliary components noted elsewhere herein.

The present compositions may be in any suitable form effective to be administered to the eye. Such forms include solutions, suspensions, ointments, gels, solids and the like. An ointment may be considered as a form intermediate between a suspension and a gel. Each of these forms of the present compositions can be prepared using techniques and processing which are conventional and well known in the art.

In another embodiment, the carrier component may be in the form of a clear material which forms a semi-solid "gel" at human body temperatures. Various polymers, many of which are conventional and well known in the art, can be included in the carrier components to provide the present compositions in the form of gels. For example, a polymer system including alkylene diamine tetra substituted with about 40% to about 80% poly(oxyethylene) units and about 20% to about 60% poly(oxypropylene) units may be employed. The molecular weight of the polymer used preferably is at least about 7,000 and can be as high as about 50,000, more preferably in the range of about 7,000 to about 30,000. The gel-forming component, if

any is present in an amount effective to provide the composition in the form of a gel. For example, such gel forming component may be present in an amount in a range of about 10% or less to about 50% or more by weight of the total carrier component.

The compositions may also be in the form of solid inserts, for example a solid dosage form that is suitable for insertion into the cul-de-sac of a mammalian eye. To this end, the composition components can be included with a non-bioerodible insert, for example, one which after dispensing the active component or components remains essentially intact, or a bio-erodible insert, for example, one that either is soluble in lacrimal fluids, or otherwise disintegrates.

A solid water soluble polymer may be employed in the carrier component. Such polymers include, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, or a hydroxy lower alkyl cellulose such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and the like; acrylates such as polyacrylic acid salts, ethyl acrylates, polyacrylamides, natural products such as gelatin, alginates, pectins, tragacanth, daraya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxyethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, mixtures thereof and the like.

In another useful embodiment, the present compositions further include a combination partner component, in addition to the benzoquinolizine-2-carboxylic acid component and the carrier component, in an amount effective to reduce inflammation and/or pain when the compositions are administered to a mammalian eye, for example, to prevent or treat diseases which are either caused by, associated with or accompanied by inflammatory processes and/or pain, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The combination partner component may be present in the present compositions in any suitable concentration effective to reduce inflammation or pain when the composition is placed in a mammalian eye.

The present compositions may be prepared using conventional techniques, for example, by formation of solutions, gels, suspensions, etc., using well known and conventional techniques. For a more detailed discussion of the preparation and administration of ophthalmic formulations see Remington's Pharmaceutical Sciences, 15 Ed., Pgs. 1489 to 1504 (1975) which is incorporated in its entirety herein by reference.

In general, the present methods for treating mammalian eyes comprise administering to the mammalian eye a therapeutically effective amount of the present composition thereby providing an effective antibiotic in the mammalian eye, and, if a combination partner component is present in the composition, thereby reducing inflammation or pain in the mammalian eye. The present methods of use may involve any suitable administration step or steps to provide an effective amount of the composition to the mammalian eye. Such administering may include, but is not limited to, topical application to the eye, instillation into the eye, placing an insert into the cul-de-sac (space) between the eyeball and the eyelid and the like. Other conventional methods of administering compositions to the eye may be employed provided that the present compositions are administered so as to provide the benefits desired.

The present use methods may be considered to be curative and/or preventative when applied, presurgically or immediately post traumatically, that is before a microbial infection develops, or before inflammation and/or pain is apparent. The present use methods are effective to reduce the risk of the formation of such infections and to reduce the severity of any inflammation or pain which may develop.

The dosage level of the present composition depends, of course, on many factors, for example, the particular application involved, the particular active component or components employed, the concentration of the active component or components in the composition, the severity of the infection/inflammation/pain and the individuals response to the treatment. Such dosage can be easily determined by routine and well known techniques to achieve the desired results in the individual patient being treated.

The following non-limiting examples illustrate certain aspects of the present invention.

Example 1

Nadifloxacin 1% and Adapalene 0.1% Cream

A) **COMPOSITION :**

Each gram of cream contains :
Nadifloxacin ..... 10.0 mg
Adapalene .....1.0 mg
In a cream base ..... q.s.

B) **FORMULA :**

No.	Ingredients	% w/w	Status of material
1	Nadifloxacin	1.00	Active
2	Adapalene	0.10	Active
3	Disodium edetate	0.10	Chelating agent
4	Propylene glycol	10.00	Humectant
5	Methyl paraben	0.18	Antimicrobial preservative
6	Propyl paraben	0.02	Antimicrobial preservative
7	Cetostearyl alcohol	7.20	Emulsifying agent, viscosity increasing agent
8	Liquid paraffin (heavy)	15.00	Emollient
9	Microcrystalline wax	3.00	Stiffening agent
10	Cetomacrogol – 1000	2.00	Emulsifying agent
11	Dimethicone	0.10	Antifoaming agent
12	α-Tocopherol	0.03	Anti-oxidant
13	Purified water	q.s. to 100.00	Solvent

Nadifloxacin 1% and Adapalene 0.1% Cream

MANUFACTURING PROCEDURE :

1) Heat and melt oil phase i.e. cetostearyl alcohol, liquid paraffin (heavy), microcrystalline wax, cetomacrogol-1000 and dimethicone and heat to 70°C.

2) Dissolve methyl paraben and propyl paraben in propylene glycol.

3) Dissolve disodium edetate in purified water and heat to 70°C.

4) Add oil phase (1) to water phase (3) under homogenization and homogenize to form emulsion.

5) Add solution (2) to emulsion (4) and cool to room temperature, add and mix α-tocopherol.

6) Triturate Nadifloxacin and Adapalene with part quantity of cream (5). Then mix with entire quantity of cream and pass through triple roller mill.

7) Fill the cream in tubes.

Example 2

Nadifloxacin 1% and Clobetasol Propionate 0.05% Cream

A) COMPOSITION :

Each gram of cream contains :
Nadifloxacin ..... 10.0 mg
Clobetasol Propionate USP ..... 0.5 mg
In a cream base ..... q.s.

B) FORMULA :

No.	Ingredients	% w/w	Status of material
1	Nadifloxacin	1.00	Active
2	Clobetasol Propionate	0.05	Active
3	Disodium edetate	0.10	Chelating agent
4	Propylene glycol	10.00	Humectant
5	Methyl paraben	0.18	Antimicrobial preservative
6	Propyl paraben	0.02	Antimicrobial preservative
7	Cetostearyl alcohol	7.20	Emulsifying agent, viscosity increasing agent
8	Liquid paraffin (heavy)	15.00	Emollient
9	Microcrystalline wax	3.00	Stiffening agent
10	Cetomacrogol – 1000	2.00	Emulsifying agent
11	Dimethicone	0.10	Antifoaming agent
12	α-Tocopherol	0.03	Anti-oxidant
13	Purified water	q.s. to 100.00	Solvent

Nadifloxacin 1% and Clobetasol Propionate 0.05% Cream

C) MANUFACTURING PROCEDURE :

1) Heat and melt oil phase i.e. cetostearyl alcohol, liquid paraffin (heavy), microcrystalline wax, cetomacrogol-1000 and dimethicone and heat to 70°C.

2) Dissolve methyl paraben and propyl paraben in part quantity of propylene glycol.

3) Dissolve clobetasol propionate in part quantity of propylene glycol.

4) Dissolve disodium edetate in purified water and heat to 70°C.

5) Add oil phase (1) to water phase (4) under homogenization and homogenize to form emulsion.

6) Add solution (2) to emulsion (5) and cool to room temperature; add and mix α-tocopherol.

7) Triturate Nadifloxacin and solution (3) with part quantity of cream (6). Then mix with entire quantity of cream and pass through triple roller mill.

8) Fill the cream in tubes.

Example 3

Nadifloxacin 1%, Butenafine Hydrochloride 1% and Clobetasol Propionate 0.05% Cream

A) COMPOSITION :

Each gram of cream contains :

Nadifloxacin ..... 10.0 mg
Butenafine Hydrochloride ..... 10.0 mg
Clobetasol Propionate USP ..... 0.5 mg
In a cream base ..... q.s.

B) FORMULA :

No.	Ingredients	% w/w	Status of material
1	Nadifloxacin	1.00	Active
2	Butenafine Hydrochloride	1.00	Active
3	Clobetasol Propionate	0.05	Active
4	Disodium edetate	0.10	Chelating agent
5	Propylene glycol	10.00	Humectant
6	Methyl paraben	0.18	Antimicrobial preservative
7	Propyl paraben	0.02	Antimicrobial preservative
8	Cetostearyl alcohol	7.20	Emulsifying agent, viscosity increasing agent
9	Liquid paraffin (heavy)	15.00	Emollient
10	Microcrystalline wax	3.00	Stiffening agent
11	Cetomacrogol – 1000	2.00	Emulsifying agent
12	Dimethicone	0.10	Antifoaming agent
13	α-Tocopherol	0.03	Anti-oxidant
14	Diethanolamine	0.30	Alkalizing agent
15	Purified water	q.s. to 100.00	Solvent

Nadifloxacin 1%, Butenafine Hydrochloride 1% and Clobetasol Propionate 0.05% Cream

C) MANUFACTURING PROCEDURE :

1) Heat and melt oil phase i.e. cetostearyl alcohol, liquid paraffin (heavy), microcrystalline wax, cetomacrogol-1000 and dimethicone and heat to 70°C.

2) Dissolve methyl paraben and propyl paraben in part quantity of propylene glycol.

3) Dissolve clobetasol propionate in part quantity of propylene glycol.

4) Dissolve disodium edetate in purified water and heat to 70°C.

5) Add oil phase (1) to water phase (4) under homogenization and homogenize to form emulsion.

6) Add solution (2) to emulsion (5) and cool to room temperature; add and mix α-tocopherol.

7) Triturate Nadifloxacin, Butenafine Hydrochloride and solution (3) with part quantity of cream (6). Then mix with entire quantity of cream, add and mix diethanolamine and pass through triple roller mill.

8) Fill the cream in tubes.

Example 4

Nadifloxacin 1%, Miconazole Nitrate 2% and Clobetasol Propionate 0.05% Cream

A) COMPOSITION :

Each gram of cream contains :
Nadifloxacin ..... 10.0 mg
Miconazole Nitrate IP ..... 20.0 mg
Clobetasol Propionate USP ..... 0.5 mg
In a cream base ..... q.s.

B) FORMULA :

No.	Ingredients	% w/w	Status of material
1	Nadifloxacin	1.00	Active
2	Miconazole Nitrate	2.00	Active
3	Clobetasol Propionate	0.05	Active
4	Disodium edetate	0.10	Chelating agent
5	Propylene glycol	10.00	Humectant
6	Methyl paraben	0.18	Antimicrobial preservative
7	Propyl paraben	0.02	Antimicrobial preservative
8	Cetostearyl alcohol	7.20	Emulsifying agent, viscosity increasing agent
9	Liquid paraffin (heavy)	15.00	Emollient
10	Microcrystalline wax	3.00	Stiffening agent
11	Cetomacrogol – 1000	2.00	Emulsifying agent
12	Dimethicone	0.10	Antifoaming agent
13	α-Tocopherol	0.03	Anti-oxidant
14	Diethanolamine	0.30	Alkalizing agent
15	Purified water	q.s. to 100.00	Solvent

Nadifloxacin 1%, Miconazole Nitrate 2% and Clobetasol Propionate 0.05% Cream

C) MANUFACTURING PROCEDURE :

1) Heat and melt oil phase i.e. cetostearyl alcohol, liquid paraffin (heavy), microcrystalline wax, cetomacrogol-1000 and dimethicone and heat to 70°C.

2) Dissolve methyl paraben and propyl paraben in part quantity of propylene glycol.

3) Dissolve clobetasol propionate in part quantity of propylene glycol.

4) Dissolve disodium edetate in purified water and heat to 70°C.

5) Add oil phase (1) to water phase (4) under homogenization and homogenize to form emulsion.

6) Add solution (2) to emulsion (5) and cool to room temperature; add and mix α-tocopherol.

7) Triturate Nadifloxacin, miconazole nitrate and solution (3) with part quantity of cream (6). Then mix with entire quantity of cream, add and mix diethanolamine and pass through triple roller mill.

8) Fill the cream in tubes.

CLAIMS

1. A composition comprising a benzoquinoline-2-carboxylic acid of formula II, a compound selected from the group consisting of a retinoid, a steroid/nonsteriod anti-inflammatory agent, an antifungal agent and an antimicrobial and an excipient/s.

Dated this 30th day of December 2002

DR N J de SOUZA
DIRECTOR-R&D